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THE SAFETY AND THERAPEUTIC EFFECTIVENESS OF NONWASHED MEDIASTINAL SHED BLOOD REINFUSED INTO PATIENTS FOLLOWING OPEN HEART SURGERY

BY

T.C. AXFORD, J.A. DEARANI, G. RAGNO, H. MacGREGOR, M.A. PATEL, C.R. VALERI, AND S.F. KHURI

NAVAL BLOOD RESEARCH LABORATORY
BOSTON UNIVERSITY SCHOOL OF MEDICINE
615 ALBANY STREET
BOSTON, MA 02118

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n=16) or liquid preserved packed red blood cells (Group 2, n=16) for transfusion (TXN) therapy of postoperative bleeding. Patient blood samples and bleeding times were obtained preoperatively, postCPB-preTXN, 2 and 24 hours postTXN, and on postoperative days 2, 3, and 7. Group 1 patients received an average of 710 ± 90 ml (range 300-1700 ml) of NSM blood containing significantly greater ($p < 0.0001$) amounts of fibrin degradation products and D-dimer protein. Of the hematologic, microaggregate, and plasma protein measurements performed, only Protein C was significantly greater ($p < 0.05$, 1 vs 2) after transfusion. Patient bleeding times were not significantly different between the groups at all time points. Total postoperative blood loss was not different between groups. There was a trend toward less need for homologous transfusion in Group 1 ($p < 0.1$). This study documents the safety, ease, and cost-saving of using nonwashed shed mediastinal blood as primary blood volume support following open heart surgery.

ABSTRACT

This prospective study was designed to determine if use of nonwashed shed mediastinal blood could exacerbate platelet and related hematologic dysfunctions following cardiopulmonary bypass (CPB) when compared to the alternative use of autologous and homologous liquid preserved blood for volume support. Thirty-two patients undergoing CPB for open heart surgery were randomized to receive either nonwashed shed mediastinal (NSM) blood (Group 1, n=16) or liquid preserved packed red blood cells (Group 2, n=16) for transfusion (TXN) therapy of postoperative bleeding. Patient blood samples and bleeding times were obtained preoperatively, postCPB-preTXN, 2 and 24 hours postTXN, and on postoperative days 2, 3, and 7. Group 1 patients received an average of 710 ± 90 ml (range 300-1700 ml) of NSM blood containing significantly greater ($p < 0.0001$) amounts of fibrin degradation products and D-Dimer protein. Of the hematologic, microaggregate, and plasma protein measurements performed, only Protein C was significantly greater ($p < 0.05$, 1 vs 2) after transfusion. Patient bleeding times were not significantly different between the groups at all time points. Total postoperative blood loss was not different between groups. There was a trend toward less need for homologous transfusion in Group 1 ($p < 0.1$). This study documents the safety, ease, and cost-saving of using nonwashed shed mediastinal blood as primary blood volume support following open heart surgery.

INTRODUCTION

Despite recent advances in the understanding of the clinical hemostatic defect produced by cardiopulmonary bypass, postoperative bleeding following cardiac surgery remains a significant source of morbidity and increases the frequency of homologous blood transfusions. Postoperative reinfusion of shed mediastinal blood has been shown to reduce homologous blood requirement while not increasing postoperative blood loss after cardiac surgery [1,2]. The loss of platelet function is considered the most important defect in the hemostatic system caused by cardiopulmonary bypass resulting in blood loss [3], and is manifested in vivo in humans in the postoperative period as a prolongation of the template bleeding time [4,5]. The postoperative bleeding time has been shown to correlate with non-surgical blood loss following cardiopulmonary bypass [6].

Transfusion of nonwashed shed mediastinal blood has been shown to increase the plasma level of fibrin degradation products in the recipient and, as such, may have potentially serious implications in the postoperative patient [7]. Platelet aggregation may be inhibited by the products of fibrinogen and fibrin degradation by binding of these products to fibrinogen and platelet membrane glycoprotein IIb/IIIa, thus interfering with the normal interaction between platelets and fibrinogen [8]. In addition, evidence from patients with acute myocardial infarction treated with tissue-type

plasminogen activator indicates that there may be a plasmin-mediated derangement of platelet aggregation in vivo, demonstrated by a prolongation of the template bleeding time, that correlates with spontaneous bleeding complications after thrombolytic therapy [9].

These data suggest two potential mechanisms of in vivo platelet dysfunction resulting from the transfusion of nonwashed shed mediastinal blood in patients following cardiac surgery. First, the contents of shed mediastinal blood may directly inhibit platelet function by interaction with platelet membrane receptors, and second, transfusion of shed mediastinal blood may activate fibrinolytic pathways, resulting in diminished platelet aggregation in vivo, as evidenced by an extension of the template bleeding time. None of the reported studies have described the effects of transfusion of nonwashed shed mediastinal blood on platelet function as determined by the bleeding time.

This prospective randomized study was designed to test the hypothesis that use of nonwashed shed mediastinal blood may exacerbate platelet dysfunction following cardiopulmonary bypass when compared to the alternative use of autologous or homologous liquid preserved blood for volume replacement. Specifically, we sought to determine if the presence of substances that inhibited platelet function in nonwashed shed mediastinal blood worsened the functional thrombocytopathy present following extracorporeal circulation. In addition,

we sought to identify any effect of shed mediastinal blood transfusion on the activation of fibrinolytic pathways in vivo. We also hoped to determine a safe range of nonwashed shed mediastinal blood which could be transfused without producing hemorrhagic complications.

PATIENTS AND METHODS

Patients. The experimental protocol for this study was approved by our institutional human research committee on February 17, 1987. Between June 1988 and August 1989, 103 patients (mean age 60 ± 1 years, range 41 to 72 years) who gave informed consent for participation in this study underwent cardiopulmonary bypass for open heart surgery at the West Roxbury Veterans Administration Medical Center. They included patients undergoing reoperations and emergency procedures as well. All operations were performed by two surgeons using identical operative and myocardial protection techniques.

Randomization Criteria. To ensure a homogeneous patient population for comparison, strict criteria for randomization were established prior to the initiation of the study. The goals of these criteria were to sample patients who were bleeding a significant amount postoperatively from non-surgical causes, and who demonstrated a need for volume expansion using red blood cell products during the immediate (< 12 hours) postoperative period. Patients who bled less

than 400 milliliters into the chest tube/Pleurevac collecting system within the first four hours following the complete reversal of heparin with protamine (as documented by return of the Activated Clotting Time (ACT) to, or below, preoperative values) were excluded from the study because in our experience these patients rarely need transfusion with red cell products in the immediate postoperative period. The decision to transfuse a patient with blood postoperatively was made by the clinician who was normally responsible for the patient's postoperative care and who was not involved with the study. The clinical criteria used to determine the need for transfusion included combinations of the following parameters: Systolic blood pressure < 80 mm Hg, mean arterial pressure < 50 mm Hg, central venous pressue < 5 mm Hg, pulmonary capillary wedge pressure < 5 mm Hg, cardiac index < 2.0 L/min/m^2, evidence of inadequate end organ perfusion (i.e., urine output < 20 ml/hr), and anemia (hematocrit < 25 vol %). There was not one of the above criteria that ensured transfusion, but rather, a clinical decision was made based on the status of each patient.

Once the decision to transfuse was made, the intensive care unit nurse was instructed, based on the preoperative randomization, to give either the volume of mediastinal shed blood that had collected up to that point, or one unit of packed red blood cells. Autologous packed cells were used if available, otherwise, homologous packed cells were transfused.

If a second or third transfusion was given in the first 24 hours following surgery, the patients who initially received shed mediastinal blood received additional shed blood, while patients who initially received banked blood received additional units of packed red cells. Patients randomized to receive shed blood whose blood requirements exceeded the amount of shed blood available or who required blood transfusions beyond 48 hours postoperatively were transfused with homologous packed red blood cells.

Procedures. Pre-anesthetic medications included intramuscular Fentanyl (100 μg), Droperidol (5 mg), and Atropine (0.4 mg). Anesthesia was induced with Fentanyl, and maintained with a combination of Fentanyl, muscle relaxants, and either Halothane or Isoflurane. Operations were performed with standard cardiopulmonary bypass at 2.4 L/min/m^2. A single two-staged cannula inserted through the atrial appendage was used for venous return, and an 8 mm cannula inserted through the ascending aorta was used for arterial perfusion. The heart was vented through the right superior pulmonary vein. Patients were cooled to a temperature range of 25-30° C depending on the complexity of the surgical procedure. The pump was primed with lactated Ringer's solution. During the period of aortic clamping, the heart was cooled with antegrade infusion of cold (4° C) cardioplegic solution and with topical ice slush to a temperature range of 8-15° C. Heparin was administered prior to institution of

cardiopulmonary bypass in an initial dose of 3 mg/kg body weight, with additional doses given to maintain the ACT above 480 seconds during extracorporeal circulation. At the end of bypass heparin was neutralized with protamine sulfate given in a ratio of 0.5 mg protamine to 1.0 mg heparin for the initial heparin dose, and 1.0 mg protamine to 1.0 mg heparin for all subsequent heparin doses. Systemic temperature was measured intraoperatively and postoperatively using a thermister in the bladder.

Blood Loss. Measurement of postoperative blood loss was started intraoperatively when the ACT had normalized after administration of protamine. This was done by collecting all the blood aspirated from the surgical field and by weighing all blood-soaked sponges. Postoperatively, an accurate hourly record was kept of all mediastinal drainage until the mediastinal drainage tubes were removed. Mediastinal shed blood was collected using the Deknatel (Fall River, MA) Pleur-evac Autotransfusion System, Model A-5005-ATS, with a Model A-1200-ATS polyvinyl chloride blood collection bag containing an in-line 200 micron nylon mesh filter through a closed system with -20 cm H_2O suction applied. This collection system contained no anticoagulant and none was added. Mediastinal shed blood was transfused without washing by detaching the autotransfusion replacement bag and reinfusing through a standard 40 micron Pall screen blood filter (Model # SQ40S, Fajardo, Puerto Rico) through a peripheral

intravenous line. For patients randomized to receive banked blood, citrate-phosphate-dextrose (CPD) ADSOL preserved cross-matched packed red blood cell units stored at 4° C for up to 42 days were used. These were infused through an identical peripheral intravenous blood administration set using the same Pall filter. Platelets were isolated from CPD blood and stored at 22° C for up to 5 days with aggitation. Platelets were transfused by pooling platelets isolated from 4-10 units of ABO compatible blood prior to transfusion.

Laboratory Procedures. Blood samples for analysis were drawn from either the unit of shed mediastinal blood collected or the unit of packed red blood cells to be transfused prior to transfusion. Patient blood samples were collected before induction of anesthesia, 20 minutes after institution of cardiopulmonary bypass, at the end of cardiopulmonary bypass, and 10 minutes after, 2 hours after, and 24 hours after transfusion with either shed mediastinal or banked blood. Additional blood samples were also drawn on postoperative days 2, 3, and 7. Blood samples were collected in K_3EDTA anticoagulant for measurement of hemoglobin (gm/dl) concentration (cyanmethemoglobin technique, Coulter hemoglobinometer, Coulter Electronics, Edison, NJ), hematocrit value (vol %), white blood cell count (x $10^3/mm^3$), platelet count (x $10^3/mm^3$, phase microscopy), and mean platelet volume (μ^3). The platelets were sized using a linear scale on a Coulter ZBI Counter with an H4 Channelyzer attachment (Coulter

Electronics, Hialeah, FL), and a 50/60 aperture. Details of these procedures and calibration routines have been reported previously [10]. Serum creatinine levels were determined using a Beckman Astra 8 serum electrolyte analyzer (Beckman Instruments, Brea, CA).

Total protein and albumin levels were measured by the Biuret reactions method of Kingsley [11]. Factor V (% normal), Factor VIII clotting protein (% normal), and fibrinogen (mg/dl) levels were measured by clotting assays using blood collected in 3.8 % sodium citrate [12]. Antithrombin III (% normal) was measured by a heparin cofactor assay with chromogenic substrate [13]. Protein C (% normal) was measured as described by Nicham, et al, using the chromogenic substrate CBS [14]. Fibronectin (μg/ml) was measured by an immunoturbidometric assay [15]. Plasminogen activity (% normal) was measured using the chromogenic substrate S-2251 as described by Friberger [16]. In vivo activation of fibrinolysis (i.e., plasmin activation) was assessed indirectly by measuring consumption of plasma antiplasmin activity (% normal) as described by Gallimore, et al [17]. Fibrin degradation products (μg/ml) were measured using a Trombowell-cotest Kit (Burroughs Wellcome Diagnostics, Greenville, NC) [18]. D-Dimer levels were measured by latex immunoassay using a monoclonal antibody as described by Mirshahi et al [19]. Whole blood microaggregates (Swank, mm Hg/gm Hb) were assessed in blood collected in K_3EDTA using a

screen filtration instrument equipped with a modified Model 800 Bently Pressure Transducer (Swank Screen Filtration Apparatus, Portland, OR) [20].

Standard template bleeding times, uncorrected for skin temperature, were performed in duplicate using the Simplate II bleeding time module (General Diagnostics, Durham, NC) according to the procedure of Babson and Babson [21]. Bleeding times were determined before the induction of anesthesia, during and at the completion of cardiopulmonary bypass, immediately before transfusion, and 10 minutes after, two hours after, and twenty-four hours after transfusion in the intensive care unit. Additional bleeding times were also determined on postoperative days 2, 3, and 7.

Clinical Parameters. Hospital mortality included all deaths occuring as a result of the cardiac operation. All patients in this study underwent ^{99}Technesium pertechnetate angiography by the first-pass technique preoperatively and 1 week postoperatively to quantitate left ventricular function [22]. Global ejection fractions were analyzed by a qualified observer not involved with the management of the patients. Diagnosis of perioperative myocardial infarction was based on the appearence of new Q waves or loss of R-waves on the ECG as interpreted by a cardiologist not involved with the study. Ventilatory support was quantitated arbitrarily as the number of hours of postoperative intubation. Postoperative low cardiac output syndrome was defined as the need for inotropic

agents for more than 48 hours or requirement of an intra-aortic balloon pump for postoperative support. Post-transfusion febrile reaction was defined as a maximum temperature of greater than 101.5° F within the first six hours after transfusion.

Data Analysis. Data are expressed as mean ± standard error of the mean (SEM). Two-way analysis of variance with a repeated measures design (MANOVA) was used to detect significant changes in variables with respect to time and type of transfusion (shed blood vs. banked blood), throughout the course of the study. When a significant change was noted by MANOVA, the paired t-test was used to identify significant differences between specific time points within a group, and either univariate analysis of variance or the student's t-test was used to detect significant differences between groups (shed vs. banked) at discrete time points. Categoric variables were analyzed between type of transfusion with either the χ^2 test (Chi-squared), or the Fisher's Exact Test for greater than 2 x 2 contingency tables. A probability level (p value) of 0.05 was considered significant for all analyses. All the statistical analyses were performed with the SAS statistical package (Cary, North Carolina) on an IBM-compatible personal computer.

RESULTS

Of the initial 103 patients, 71 exclusions were made from

the study. Twenty-nine patients did not bleed the required 400 ml in the first 4 hours following protamine reversal, and none of these patients were subsequently transfused for the indication of acute blood volume expansion within 12 hours of their operation. Thirty patients who bled 400 ml were not considered in need of a transfusion based on their hemodynamic data, and were thus excluded. Five patients had received aspirin within 24 hours before their operation as part of an unrelated study and were excluded. Two patients required reoperation for bleeding within the first 24 hours and had an identifiable surgical cause for their bleeding, hence they were excluded. One patient required a postoperative left ventricular assist device with anticoagulation, and another patient had his right ventricle injured during sternotomy and experienced a large associated blood loss. Three patients died within 24 hours of their operations from low cardiac output and intractable heart failure. Thus, 32 patients ultimately completed the study and were included in the data analysis. Sixteen patients were randomized to receive nonwashed shed mediastinal blood (Group 1), and 16 patients received banked blood (Group 2) for their initial transfusion therapy.

Procedures were performed for isolated coronary (n=23), valvular (n=4), and combined (n=5) disease. Patient characteristics are shown in Table 1. There were no significant differences between Group 1 and Group 2 with

respect to patient age, type of procedure performed, preoperative or postoperative left ventricular ejection fraction, duration of cardiopulmonary bypass, duration of aortic cross-clamping, frequency of postoperative myocardial infarction, need for postoperative ventilatory support, frequency of low cardiac output syndrome, or post-transfusion febrile reaction. In addition, there were no significant differences in serum creatinine levels (mg/dl) between the two groups preoperatively (1.2 ± 0.1, Group 1, 1.1 ± 0.1, Group 2), 24 hours after transfusion (1.3 ± 0.1, Group 1, 1.2 ± 0.1, Group 2), or seven days after transfusion (1.2 ± 0.1, Group 1, 1.2 ± 0.1, Group 2).

Analysis of blood units transfused. The average time to transfusion after onset of collection of the first unit of shed mediastinal blood in Group 1 was 2.4 ± 0.2 hours. The average length of storage at 4° C of the first unit of packed red blood cells transfused to each patient in Group 2 was 17 ± 2 days. The average volume of the first shed mediastinal blood transfusion given to patients in Group 1 was 453 ± 34 ml, range 300-840 ml. The average volume of total shed mediastinal blood received in Group 1 patients was 710 ± 90 ml, range 300-1700 ml. Table 2 summarizes the results of the in vitro analysis of each unit of shed mediastinal blood and ADSOL preserved banked blood prior to transfusion into the patient. These data demonstrate that, compared to nonwashed shed mediastinal blood, banked blood has a significantly

greater ($p < 0.005$) hematocrit, cellular hemoglobin content, and platelet count; whereas shed blood has greater amounts ($p < 0.01$) of Factor VIIIc activity, anti-thrombin III activity, protein C, plasminogen activity, and anti-plasmin activity. Shed and banked blood contain comparable levels of plasma hemoglobin, fibrinogen, and fibronectin. In addition, the amount of particulate microaggregates, measured as the Swank screen filtration pressure, is the same in both shed and banked blood. The level of fibrin degradation products (FDP) in shed and banked units of blood is shown in Figure 1. All measured units of banked blood had low levels of fibrin degradation products, FDP < 20 μg/ml, n = 9; while all measured units of nonwashed shed mediastinal blood had elevated levels, FDP = 20-80 μg/ml, n = 5, FDP = 80-320 μg/ml, n = 8, (Fisher's Exact $p < 0.0001$). The level of D-Dimer in shed and banked units of blood is shown in Figure 2. Likewise, all measured units of banked blood had low levels of D-Dimer (< 0.5 μg/ml, n = 11) while all measured units of nonwashed shed blood had elevated levels (D-Dimer > 2.0 μg/ml, n = 12, Fischer's Exact $p < 0.0001$).

Hematologic parameters. Table 3 shows the results for selected hematologic parameters measured during the study. There were no significant differences in any of the parameters at baseline between Group 1 and Group 2. The hematocrit fell significantly ($p < 0.05$) with the initiation of bypass from above 34 % to 23-24 % in both groups, and rose gradually in

the postoperative period reaching 28.5 ± 1.4 % in Group 1 and 28.5 ± 0.9 % in Group 2 on the seventh postoperative day. Similiarly, the platelet count fell on cardiopulmonary bypass (CPB) from around 200,000/mm^3 to approximately 100,000/mm^3 at the completion of bypass and rose gradually in the postoperative period above 270,000/mm^3 by postoperative day seven (Table 3). Neither the hematocrit, nor the platelet count were significantly different between the two groups at any time point in the study. Likewise, cellular hemoglobin levels were not significantly different between Group 1 and Group 2 for the entire study (Table 3). The plasma hemoglobin level increased significantly ($p < 0.05$) in both groups on CPB from between 7-8 mg/dl preoperatively to approximately 60-70 mg/dl at the end of CPB, and then fell rapidly ($p < 0.05$) in the immediate postoperative period to 27.5 ± 3.2 mg/dl in Group 1 and 18.3 ± 4.1 mg/dl in Group 2 by ten minutes after the first transfusion. Plasma hemoglobin levels returned to baseline levels by postoperative day 1 in both groups and, throughout the study were never significantly different between the two groups (Table 3). White blood cell counts rose significantly ($p < 0.05$) in both groups on CPB from approximately 6,000/mm^3 preoperatively to 10-12,000/mm^3 at the end of CPB, and remained slightly elevated in both groups throughout the study. These counts were, however, never significantly different between the two groups throughout the study (Table 3). Plasma microaggregate levels assessed by

Swank screen filtration pressure, referred to as SWANK, did not increase significantly (p = n.s.) in either group following the end of CPB to the time point 2 hours after transfusion (Group 1: 6.8 ± 1.0 mm Hg/g Hb to 12.4 ± 2.6 mm Hg/g Hb, p = 0.08; Group 2: 10.6 ± 2.7 mm Hg/g Hb to 17.5 ± 4.0 mm Hg/g Hb, p = 0.10); and SWANK levels were not significantly different between the two groups at any of the study timepoints. SWANK levels never increased significantly above baseline in either group for the duration of the study (Table 3). Mean platelet volume decreased significantly ($p < 0.05$) in both groups on CPB (Group 1: 8.3 ± 0.3 μ^3 to 7.7 ± 0.2 μ^3, Group 2: 8.0 ± 0.3 μ^3 to 7.3 ± 0.3 μ^3) indicating the elimination of large platelets by the bypass circuit, and then increased to baseline levels by the first postoperative day in both groups. The platelet kinetics indicated by these changes in platelet volume were identical in both groups for each timepoint during the study.

Plasma protein parameters. Table 4 shows the results for selected plasma protein parameters measured during the study. There were no significant differences in any of the parameters at baseline between Group 1 and Group 2. Factor V activity fell significantly ($p < 0.05$) with the initiation of CPB (Group 1: 71 ± 5 % to 26 ± 3 %, Group 2: 69 ± 4 % to 26 ± 2 %,) and then rose gradually in the postoperative period to reach baseline levels by the third postoperative day. These levels were never significantly different between the two

groups throughout the study. Factor VIII clotting activity also fell significantly ($p < 0.05$) with the initiation of CPB (Group 1: 85 ± 9 % to 56 ± 6 %, Group 2: 80 ± 8 % to 59 ± 8 %), but postoperatively these levels rose quickly in both groups and were significantly greater ($p < 0.05$) than preoperative levels by the third postoperative day. These levels remained significantly elevated ($p < 0.05$) in both groups for the remainder of the study with values of 205 ± 18 % in Group 1 and 150 ± 22 % in Group 2 on the seventh postoperative day (Table 4). Factor VIII clotting activity levels were never significantly different between the two groups at all timepoints throughout the study. Fibrinogen levels behaved similiar to Factor VIII levels by falling significantly ($p < 0.05$) on CPB, and then increasing postoperatively to levels above baseline ($p < 0.05$) by the second postoperative day in both groups. These levels remained elevated for the remainder of the study, but were never significantly different between the two groups at any timepoint throughout the study (Table 4). Antithrombin III levels and fibronectin levels behaved in a similiar manner, again falling significantly ($p < 0.05$) with the initiation of CPB, and then gradually increasing in the postoperative period to preoperative levels by the seventh postoperative day in both groups. These levels were never significantly different between the two groups for the entire study (Table 4). Protein C levels fell significantly in both groups ($p < 0.05$)

on CPB (Group 1: 112 ± 7 % to 65 ± 5 %, Group 2: 102 ± 5 % to 67 ± 5 %). However, in contrast to the other proteins, the level of Protein C was significantly greater ($p < 0.05$) in Group 1 (72 ± 4 %) compared to Group 2 (63 ± 2 %) two hours after transfusion. These differences were no longer significant by the first postoperative day, and the level of Protein C remained below baseline in both groups until the seventh postoperative day (Table 4). Except for Protein C, all measured plasma protein levels were not significantly changed by transfusion with either nonwashed shed mediastinal blood or liquid preserved packed cells during this study.

Bleeding time and fibrinolytic parameters. Table 5 shows the results for the bleeding time, not corrected for skin temperature, and plasma fibrinolytic parameters measured during the study. The bleeding time was not significantly different between the two groups at baseline. The bleeding time increased in both groups with the initiation of CPB, and remained significantly elevated ($p < 0.05$) in both groups at the end of CPB (Group 1: 7.5 ± 0.5 min to 14.7 ± 1.3 min, Group 2: 8.4 ± 0.6 min to 14.3 ± 1.3 min). The bleeding time gradually corrected in the immediate perioperative period, however, it remained elevated ($p < 0.05$) in both groups two hours after transfusion (Group 1: 10.0 ± 1.1 min, Group 2: 10.7 ± 0.7 min). The bleeding time returned to baseline levels in both groups by the first postoperative day. The bleeding time was never significantly different between the

two groups at each timepoint throughout the study and was not affected by transfusion by either nonwashed shed mediastinal or banked blood (Table 5). Plasminogen levels were not significantly different at baseline between the two groups. Plasminogen levels fell significantly ($p < 0.05$) in both groups with initiaion of CPB, and gradually rose in the postoperative period, returning to baseline levels by the seventh postoperative day. The plasminogen levels were never significantly different between the two groups at every timepoint during the study including two hours after transfusion (Table 5). Plasma antiplasmin levels were significantly different ($p < 0.05$) at baseline between Group 1 (78 ± 3 %) and Group 2 (71 ± 2 %), probably representing an experimental population sampling error as opposed to any real intergroup difference. Antiplasmin levels decreased significantly ($p < 0.05$) in both groups with initiation of CPB, and remained significantly lower ($p < 0.05$) in Group 2 (45 ± 2 %) compared to Group 1 (57 ± 4) at the end of CPB. The antiplasmin levels in both groups were unaffected by transfusion, and returned to preoperative levels by the second postoperative day at which point they were no longer significantly different from one another. Antiplasmin levels increased significantly ($p < 0.05$) in similiar fashion in both groups for the remainder of the study and were not significantly different between the two groups (Table 5).

Blood loss and blood product use. Table 6 shows the

results of blood loss and blood product utilization during the study. There were no significant differences in blood loss between the two groups either from the end of protamine administration until the start of the first transfusion with shed mediastinal or banked blood (Group 1: 888 ± 79 ml, Group 2: 1001 ± 98 ml), or during the first two hours after the first transfusion (Group 1: 184 ± 40 ml, Group 2: 304 ± 107 ml), or for the total blood loss in the postoperative period (Group 1: 2016 ± 150 ml, Group 2: 2211 ± 363 ml). There were no significant differences in total blood volume replacement with colloid solutions between the two groups in either the first 24 hours postoperatively (Group 1: 1616 ± 340 ml, Group 2: 1694 ± 514 ml), or the first seven days postoperatively (Group 1: 1891 ± 362 ml, Group 2: 1803 ± 522 ml). There were no significant differences in specific blood product replacement between the two groups including fresh frozen plasma and platelets (Table 6), however the need for red blood cell transfusion trended toward fewer units transfused in patients who also received shed mediastinal blood (Group 1: 2.0 ± 0.5 units, Group 2: 3.3 ± 0.6 units, $p < 0.1$). A graphic representation of the distribution of the type of red blood cell products received during this study is shown in Figure 3. Only one patient in Group 1 received autologous blood when requiring additional transfusion therapy and this patient also subsequently received a unit of homologous blood. Five patients in Group 2 received autologous blood for their

initial transfusion therapy and three of these patients required additional transfusion with homologous blood. In all, six of sixteen patients (38 %) who received shed mediastinal blood (Group 1) were not subsequently transfused with homologous blood, while only two of sixteen patients (13 %) who received banked blood (Group 2) did not receive a homologous transfusion during this study. Again, this trended toward, but did not reach, statistical significance (Chi-squared, $p < 0.1$).

COMMENT

This prospective study was designed to study the effect of nonwashed shed mediastinal blood transfusion as compared to liquid preserved banked blood transfusion on in-vivo platelet and related hematologic functions following cardiopulmonary bypass for open heart surgery. Methods to minimize the use of homologous blood replacement postoperatively in the cardiac surgery patient population are being actively investigated because of the increased concern of the risks of blood transfusion [23-26]. In addition, the risks of febrile and hemolytic transfusion reactions, as well as the diminishing supply and high cost of homologous banked blood have further stimulated the search for the optimal blood volume management strategy in cardiac surgery [27,28]. Current techniques utilized to minimize homologous blood usage include: 1) preoperative donation of autologous blood, 2) a bloodless crystalloid pump prime, 3) salvage of all blood

removed by cardiotomy suction, 4) retrieval and reinfusion of all red blood cells remaining in the extracorporeal circuit following bypass, 5) complete surgical hemostasis, 6) postoperative volume expansion with crystalloid solutions, and 7) acceptance of postoperative anemia in the asymptomatic patient [29-31]. The postoperative reinfusion of shed mediastinal blood has been extensively studied to determine the utility of this readily available source of autologous blood and has been shown to reduce homologous blood requirement while not increasing blood loss following cardiac surgery [1,2,30].

The results of this study are consistent with previous studies that have shown the composition of nonwashed shed mediastinal blood to include a hematocrit of 20 vol %, an elevated plasma hemoglobin level of 312 mg/dl, low levels of platelets (22,000 /mm^3), extremely low levels of fibrinogen, high levels of fibrin degradation products, and decreased levels of Factor VIII clotting activity [1,27,30,32]. In addition, this study has demonstrated that nonwashed shed mediastinal blood contains decreased levels of anti-thrombin III, protein C, plasminogen, and anti-plasmin activity; although these levels are greater in shed mediastinal blood than in banked red blood cell units. These data show that shed mediastinal blood has undergone extensive coagulation and clot lysis within the mediastinum and pleural spaces before collection, consistent with recent reports [33].

The data from this study are consistent with data from Schaff, et al. [1], and Johnson, et al. [2], where comparison of transfusion with shed mediastinal blood to homologous banked blood demonstrated no difference in postoperative blood loss, consumption of plasma coagulation factors, or evidence of bleeding complications attributable to the use of mediastinal blood. These authors were able to demonstrate a reduction in homologous blood requirement in the group receiving shed mediastinal blood which our data did not show. Hartz, et al. [33], demonstrated no significant increase in by-products of fibrinogen consumption or fibrinolysis after transfusion with shed mediastinal blood, indicating no evidence for induction of either disseminated intravascular coagulation or increased fibrinolysis. The data from the present study also support this hypothesis, as we failed to demonstrate activation of fibrinolytic pathways in vivo as evidenced by consumption of clotting factors, plasminogen, or antiplasmin in response to transfusion with nonwashed shed mediastinal blood. Our data suggest that Protein C levels (a natural anticoagulant and profibrinolytic system) can be increased in patients receiving nonwashed shed mediastinal blood, however the functional significance of this finding is unknown, and this did not lead to any apparent bleeding complications.

The proposed mechanisms responsible for platelet dysfunction following cardiopulmonary bypass are

multifactorial and involve platelet activation via degranulation through contact with synthetic surfaces [4], membrane fragmentation, and loss of expression of membrane glycoprotein receptors responsible for normal platelet vessel wall adhesion and aggregation [3]. Specifically, the amounts of platelet membrane glycoprotein Ib and platelet membrane fibrinogen receptors associated with the glycoprotein IIb/IIIa complex are reduced [34,35]. These alterations in platelet membrane receptor number are thought to contribute to the platelet dysfunction produced by cardiopulmonary bypass [3,5,34]. These assertions are supported by the observations that the serine proteinase inhibitor aprotinin appears to diminish the extension in bleeding time after cardiopulmonary bypass and reduce postoperative blood loss while preserving platelet membrane glycoprotein Ib [23,36,37]. Our data demonstrated that transfusion with nonwashed shed mediastinal blood produces no additional loss of platelet fuction in excess of that present normally following cardiopulmonary bypass. Specifically, there was no evidence for increased in vivo platelet dysfunction as assessed by measurement of the template bleeding time in the group that received nonwashed shed mediastinal blood that contained high levels of fibrin degradation products and D-Dimer protein.

The results of this study indicate that transfusion of approximately 700 ml, of nonwashed shed mediastinal blood is both safe and cost-effective. The results of this study do

not apply to transfusion with massive amounts of shed mediastinal blood (> 2000 ml) which may be injurious. However, the use of modest amounts of mediastinal blood should be routinely employed as a source of autologous blood for transfusion and blood volume support in the management of postoperative cardiac surgery patients.

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The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or Naval Service at large.

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TABLE 1: PRE AND POSTOPERATIVE CHARACTERISTICS OF PATIENTS

	GROUP 1 n = 16	GROUP 2 n = 16	p
AGE (YEARS)	60 ± 2	61 ± 2	ns
PROCEDURE			
CABG	11	12	ns
VALVE	1	3	
VALVE & CABG	4	1	
RVG EJECTION FRACTION			
PREOPERATIVE (%)	48 ± 2	46 ± 2	ns
POSTOPERATIVE (%)	50 ± 3	53 ± 2	ns
CARDIOPULMONARY BYPASS			
TOTAL CPB TIME (MIN)	161 ± 19	143 ± 10	ns
CROSS-CLAMP TIME (MIN)	86 ± 12	67 ± 8	ns
POSTOPERATIVE MI	1 / 16	0 / 16	ns
DURATION OF INTUBATION (HOURS)	29 ± 3	24 ± 2	ns
LOW CARDIAC OUTPUT SYNDROME	3 / 16	2 / 16	ns
POST-TRANSFUSION FEBRILE REACTION	1 / 16	1 / 16	ns

Group 1 = Transfused with nonwashed shed mediastinal blood
Group 2 = Transfused with banked red blood cells
Values expressed as mean ± standard error of mean
CABG = Coronary Artery Bypass Grafting
CPB = Cardiopulmonary Bypass
MI =Myocardial Infarction
RVG = Radioventriculogram
VALVE = Aortic or Mitral valve replacement

TABLE 2: IN VITRO BLOOD UNIT ANALYSIS

	SHED	BANKED	p
HEMOGLOBIN (gm/dl)	7.9 ± 0.4	19.2 ± 0.9	0.0001
HEMATOCRIT (vol %)	19 ± 1	55 ± 3	0.0001
PLASMA HEMOGLOBIN (mg/dl)	312 ± 32	198 ± 87	ns
WHITE BLOOD CELLS ($x10^3/mm^3$)	4.5 ± 0.4	7.3 ± 2.0	ns
PLATELET COUNT ($x10^3/mm^3$)	22 ± 9	118 ± 29	0.005
FACTOR VIIIc (%)	25 ± 4	0 ± 0	0.0001
FIBRINOGEN (mg/dl)	26 ± 11	42 ± 9	ns
ANTI-THROMBIN III (%)	33 ± 4	19 ± 3	0.01
PROTEIN C (%)	71 ± 7	22 ± 3	0.0001
FIBRONECTIN (µg/ml)	112 ± 16	89 ± 13	ns
PLASMINOGEN (%)	57 ± 3	26 ± 1	0.0001
ANTI-PLASMIN (%)	39 ± 2	20 ± 2	0.0001
SWANK (mmHg/gmHb)	16 ± 4	64 ± 23	ns

SHED = Nonwashed shed mediastinal blood
BANKED = Liquid preserved packed red blood cells
Values expressed as mean ± standard error of mean

TABLE 3: HEMATOLOGIC PARAMETERS OF PATIENTS

VARIABLE	HEMATOCRIT (vol %)		HEMOGLOBIN (g/dl)		PLASMA HEMOGLOGIN (mg/dl)	
GROUP	1	2	1	2	1	2
PRE-OP	34.3 ± 1.3	34.6 ± 1.3	11.7 ± 0.5	11.6 ± 0.5	7.7 ± 1.4	7.0 ± 0.8
ON CPB	24.0 ± 1.2	22.8 ± 0.8	8.0 ± 0.4	7.6 ± 0.3	25.1 ± 3.1	27.4 ± 4.8
END CPB	25.0 ± 0.9	25.7 ± 1.0	8.9 ± 0.3	8.4 ± 0.4	62.3 ± 6.9	72.8 ± 8.8
10 MIN POST-TXN	30.2 ± 1.2	30.9 ± 1.0	10.3 ± 0.5	10.7 ± 0.3	27.5 ± 3.2	18.3 ± 4.1
2 HOURS POST-TXN	28.7 ± 1.5	30.1 ± 1.1	9.7 ± 0.5	10.3 ± 0.5	13.1 ± 2.2	8.2 ± 1.5
POST OP DAY 1	26.9 ± 0.9	24.5 ± 1.1	9.3 ± 0.3	8.9 ± 0.3	5.2 ± 1.9	4.8 ± 2.7
POST OP DAY 2	26.3 ± 0.9	25.7 ± 0.9	8.7 ± 0.4	8.8 ± 0.4	6.2 ± 2.3	4.9 ± 2.2
POST OP DAY 3	27.1 ± 0.9	25.6 ± 1.0	9.3 ± 0.4	8.6 ± 0.4	4.6 ± 1.4	11.2 ± 5.3
POST OP DAY 7	28.5 ± 1.4	28.5 ± 0.9	9.7 ± 0.5	9.7 ± 0.3	2.1 ± 0.5	10.5 ± 4.9

VARIABLE	WBC ($x10^3/mm^3$)		PLATELET COUNT ($x10^3/mm^3$)		SWANK (mmHg/gHb)	
GROUP	1	2	1	2	1	2
PRE-OP	6.4 ± 0.4	5.8 ± 0.5	200 ± 19	191 ± 11	8.0 ± 1.0	12.9 ± 3.5
ON CPB	4.5 ± 0.5	4.0 ± 0.4	98 ± 12	94 ± 6	6.5 ± 0.8	7.6 ± 1.0
END CPB	12.1 ± 1.1	10.2 ± 0.9	104 ± 12	109 ± 8	6.8 ± 1.0	10.6 ± 2.7
10 MIN POST-TXN	12.9 ± 1.3	9.9 ± 0.9	129 ± 17	113 ± 14	9.3 ± 1.8	10.7 ± 2.2
2 HOURS POST-TXN	12.1 ± 1.1	10.1 ± 0.9	138 ± 16	108 ± 8	12.4 ± 2.6	17.5 ± 4.0
POST OP DAY 1	10.5 ± 0.9	8.4 ± 0.7	127 ± 14	107 ± 9	10.9 ± 2.2	15.0 ± 4.1
POST OP DAY 2	11.4 ± 0.9	10.3 ± 0.6	116 ± 14	114 ± 12	14.0 ± 3.0	14.8 ± 5.3
POST OP DAY 3	11.8 ± 1.0	10.7 ± 0.7	149 ± 16	122 ± 12	11.6 ± 3.3	12.6 ± 2.6
POST OP DAY 7	11.0 ± 0.9	9.7 ± 0.8	271 ± 42	284 ± 27	9.0 ± 0.8	10.9 ± 1.7

Group 1 = Transfused with nonwashed shed mediastinal blood
Group 2 = Transfused with banked red blood cells
Values expressed as mean ± standard error of mean
CPB = Cardiopulmonary Bypass
SWANK = Microaggregate screen filtration pressure
TXN = Transfusion
WBC = White blood cell count

TABLE 4: PROTEIN PARAMETERS OF PATIENTS

VARIABLE	FACTOR V ACTIVITY (%)		FACTOR VIII CLOTTING ACTIVITY (%)		FIBRINOGEN (mg/dl)	
GROUP	1	2	1	2	1	2
PRE-OP	71 ± 5	69 ± 4	85 ± 9	80 ± 8	319 ± 19	336 ± 24
ON CPB						
END CPB	26 ± 3	26 ± 2	56 ± 6	59 ± 8	200 ± 16	191 ± 12
10 MIN POST-TXN	28 ± 3	28 ± 2	50 ± 5	69 ± 8	207 ± 19	232 ± 22
2 HOURS POST-TXN	29 ± 3	26 ± 2	54 ± 6	63 ± 8	209 ± 15	234 ± 19
POST OP DAY 1	47 ± 6	37 ± 2	117 ± 16	90 ± 11	360 ± 22	334 ± 27
POST OP DAY 2	53 ± 4	52 ± 3	105 ± 10	116 ± 12	455 ± 39	478 ± 37
POST OP DAY 3	72 ± 11	64 ± 5	165 ± 27	140 ± 18	571 ± 37	503 ± 39
POST OP DAY 7	63 ± 6	72 ± 12	205 ± 18	150 ± 22	539 ± 51	482 ± 44

VARIABLE	ANTITHROMBIN III (%)		FIBRONECTIN (µg/ml)		PROTEIN C (%)	
GROUP	1	2	1	2	1	2
PRE-OP	90 ± 4	81 ± 4	343 ± 21	339 ± 26	112 ± 7	102 ± 5
ON CPB	56 ± 6	49 ± 3	228 ± 32	153 ± 15		
END CPB	56 ± 4	54 ± 3	219 ± 16	205 ± 18	65 ± 5	67 ± 5
10 MIN POST-TXN	63 ± 4	55 ± 2	207 ± 21	178 ± 22	74 ± 6	66 ± 3
2 HOURS POST-TXN	62 ± 3	55 ± 3	204 ± 18	215 ± 25	72 ± 4 *	63 ± 2
POST OP DAY 1	59 ± 4	54 ± 3	199 ± 14	165 ± 22	65 ± 4	57 ± 3
POST OP DAY 2	61 ± 4	55 ± 3	201 ± 23	208 ± 29	65 ± 5	62 ± 4
POST OP DAY 3	75 ± 6	63 ± 5	239 ± 35	220 ± 44	66 ± 7	67 ± 4
POST OP DAY 7	81 ± 9	88 ± 8	339 ± 38	405 ± 63	79 ± 10	75 ± 10

Group 1 = Transfused with nonwashed shed mediastinal blood
Group 2 = Transfused with banked red blood cells
Values expressed as mean ± standard error of mean
* ANOVA $p < 0.05$
CPB = Cardiopulmonary Bypass
TXN = Transfusion

TABLE 5: BLEEDING TIME AND FIBRINOLYTIC PARAMETERS OF PATIENTS

VARIABLE	BLEEDING TIME (min)		PLASMINOGEN (%)		ANTIPLASMIN (%)	
GROUP	1	2	1	2	1	2
PRE-OP	7.5 ± 0.5	8.4 ± 0.6	80 ± 3	81 ± 4	78 ± 3	71 ± 2
ON CPB	>20 ± 0	>20 ± 0	57 ± 7	49 ± 7		
END CPB	14.7 ± 1.3	14.3 ± 1.3	50 ± 3	56 ± 4	57 ± 4	45 ± 2
10 MIN POST-TXN	10.4 ± 1.0	11.1 ± 1.1	60 ± 5	55 ± 2	58 ± 3	51 ± 3
2 HOURS POST-TXN	10.0 ± 1.1	10.7 ± 0.7	56 ± 3	53 ± 3	58 ± 2	49 ± 3
POST OP DAY 1	9.3 ± 0.8	9.3 ± 0.7	52 ± 3	48 ± 3	70 ± 3	61 ± 3
POST OP DAY 2	8.2 ± 0.8	8.9 ± 0.6	50 ± 4	48 ± 3	85 ± 4	78 ± 2
POST OP DAY 3	7.3 ± 0.8	6.0 ± 0.5	66 ± 7	60 ± 5	101 ± 5	90 ± 5
POST OP DAY 7	6.1 ± 0.3	5.8 ± 0.4	77 ± 5	84 ± 5	97 ± 8	89 ± 2

Group 1 = Transfused with nonwashed shed mediastinal blood
Group 2 = Transfused with banked red blood cells
Values expressed as mean ± standard error of mean
CPB = Cardiopulmonary Bypass
TXN = Transfusion

TABLE 6: BLOOD LOSS AND BLOOD PRODUCT USE OF PATIENTS

	GROUP 1	GROUP 2	p
BLOOD LOSS			
FROM PROTAMINE TO TXN (ml)	888 ± 79	1001 ± 98	ns
FIRST 2 HOURS AFTER TXN (ml)	184 ± 40	304 ± 107	ns
TOTAL POSTOPERATIVE (ml)	2016 ± 150	2211 ± 363	ns
TOTAL COLLOID VOLUME REPLACEMENT			
FIRST 24 HOURS POSTOPERATIVE (ml)	1616 ± 340	1694 ± 514	ns
7 DAYS POSTOPERATIVE (ml)	1891 ± 362	1803 ± 522	ns
SPECIFIC BLOOD PRODUCT REPLACEMENT			
PACKED RED BLOOD CELLS (units)	2.0 ± 0.5	3.3 ± 0.6	ns
FRESH FROZEN PLASMA (units)	2.0 ± 0.7	3.3 ± 1.3	ns
PLATELETS (units)	4.6 ± 2.7	5.2 ± 1.8	ns

Group 1 = Transfused with nonwashed shed mediastinal blood
Group 2 = Transfused with banked red blood cells
Values expressed as mean ± standard error of ,mean
CABG = Coronary Artery Bypass Grafting
TXN = Transfusion

LEGENDS TO FIGURES

Figure 1. The level of fibrin degradation product in shed nonwashed autologous mediastinal blood and liquid preserved autologous and homologous blood.

Figure 2. The level of D-Dimer in shed nonwashed autologous mediastinal blood and liquid preserved autologous and homologous blood.

Figure 3. The volume of autologous shed mediastinal blood and autologous and homologous liquid preserved blood transfused into patients during the first week following open heart surgery.

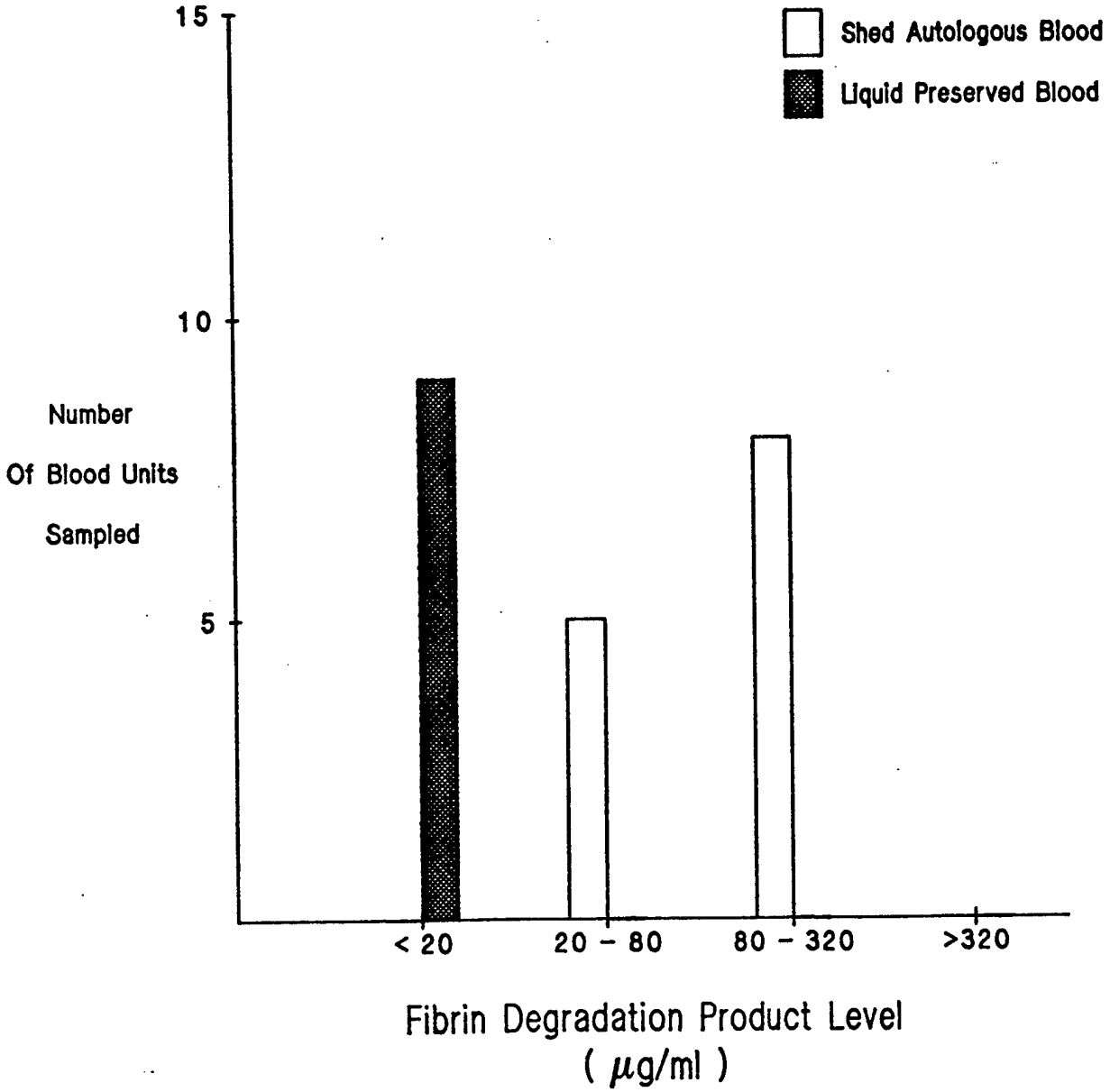
15
10
5
Number
Of Blood Units
Sampled
Shed Autologous Blood
Liquid Preserved Blood
< 20
20 - 80
80 - 320
>320
Fibrin Degradation Product Level
(μg/ml)

Fig 1.

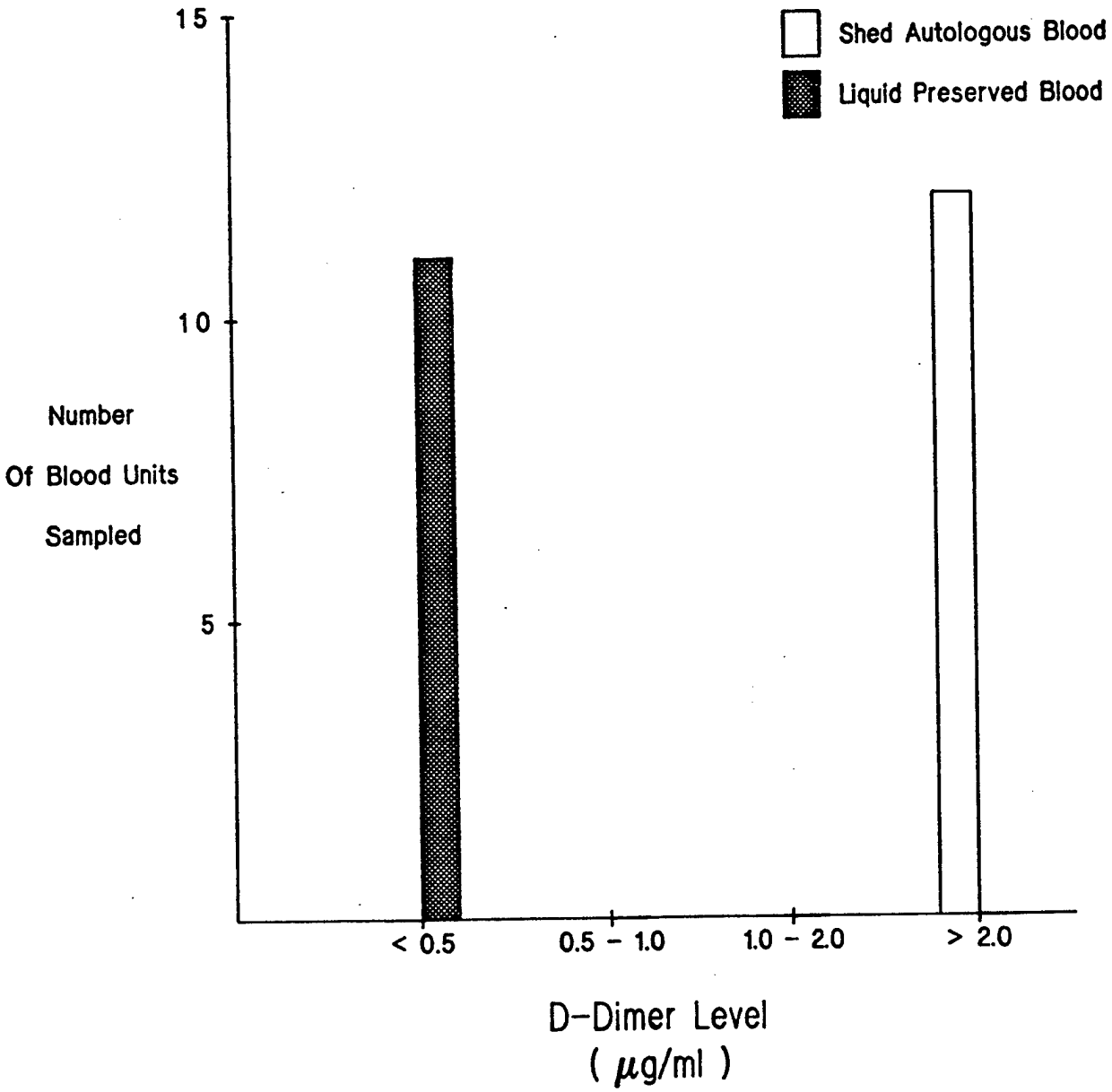
15
10
5
Number
Of Blood Units
Sampled
Shed Autologous Blood
Liquid Preserved Blood
< 0.5
0.5 – 1.0
1.0 – 2.0
> 2.0
D-Dimer Level
(μg/ml)

Fig 2.

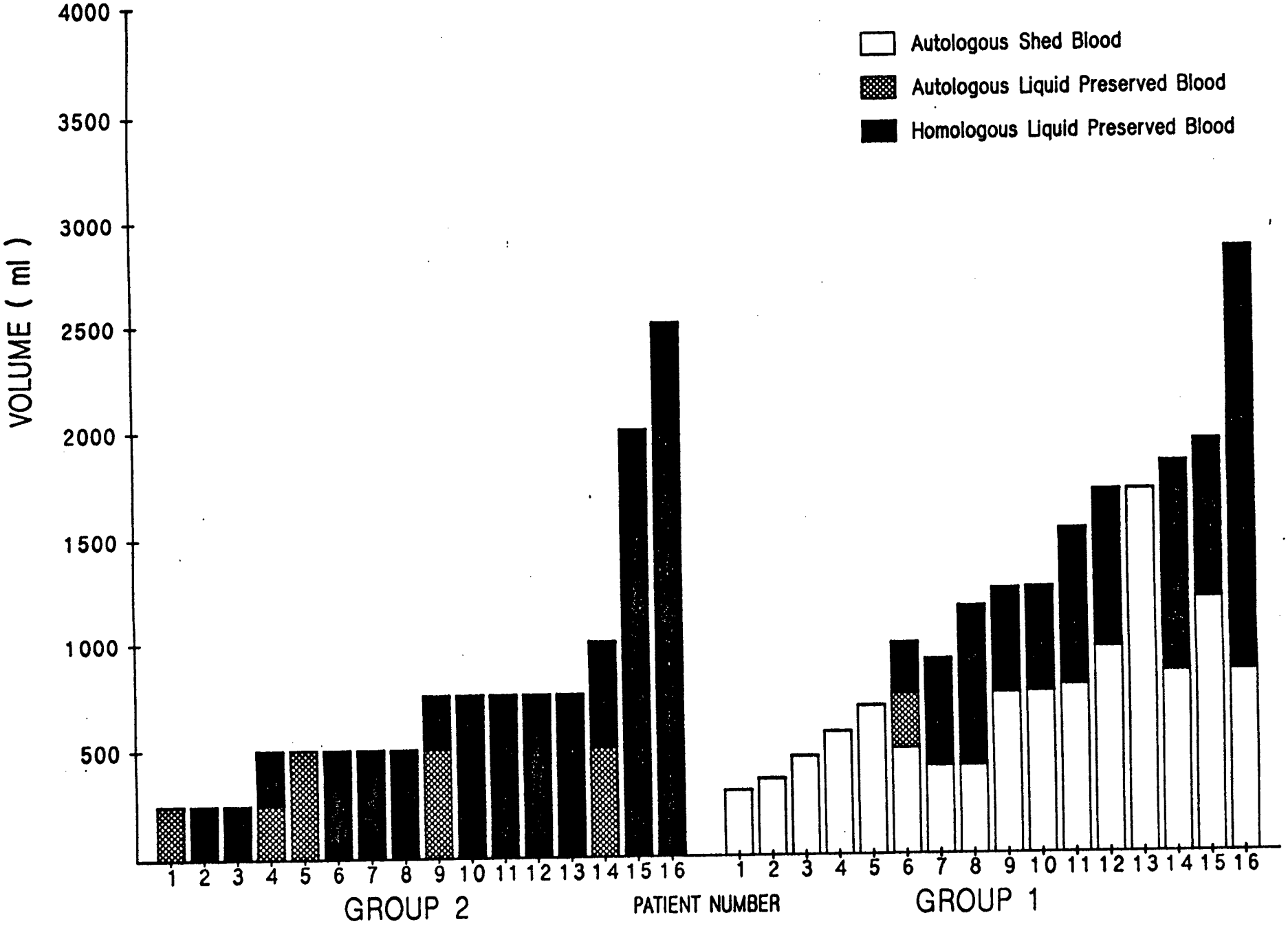
Autologous Shed Blood
Autologous Liquid Preserved Blood
Homologous Liquid Preserved Blood
VOLUME (ml)
4000
3500
3000
2500
2000
1500
1000
500
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
GROUP 2
PATIENT NUMBER
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
GROUP 1

Fig. 3